

AMENDMENTS TO THE SPECIFICATION

Please replace the paragraph beginning at page 3, line 8, with the following rewritten paragraph:

Studies of prostate cancer have revealed that PPAR γ is significantly expressed in primary prostate cancer but at very low levels in normal prostate tissue, making it a promising candidate for molecular therapy (Segawa, Y. et al., "Expression of Peroxisome Proliferator-Activated Receptor (PPAR) in Human Prostate Cancer," *Prostate*, Vol. 51, p. 108-116 (2002)). Furthermore, hemizygous deletion of PPAR γ is common in primary human prostate cancers, suggesting that loss of function may contribute to the malignant phenotype (Mueller, E. et al., "Effects of Ligand Activation of Peroxisome Proliferator-Activated Receptor γ in Human Prostate Cancer," *Proc. Natl. Acad. Sci. USA*, Vol. 97, No. 20, p. 10990-10995 (2000)). In accordance with this observation, it was found that PPAR γ activation with synthetic ligands downregulates prostate specific antigen (PSA) mRNA expression in prostate cancer cells *in vitro* (Hisatake, J.I. et al., "Down-Regulation of Prostate-Specific Antigen Expression by Ligands for Peroxisome Proliferator-Activated Receptor γ Human Prostate Cancer," *Cancer Res.*, Vol. 60, p. 5494-5498 (2000); Kubota, T. et al., "Ligand for Peroxisome Proliferator-Activated Receptor γ (Troglitazone) has Potent Antitumor Effect Against Human Prostate Cancer Both *In vitro* and *In vivo*," *Cancer Res.*, Vol. 58, p. 3344-3352 (1998)). Specifically, PPAR γ ligands, troglitazone, rosiglitazone and 15-deoxy-12,14-prostaglandin J2 have demonstrated growth inhibition of prostate cancer cell lines that express an appreciable level of PPAR γ (Mueller et al., 2000; Segawa et al., "Expression of peroxisome proliferator-activated receptor (PPAR) in human prostate cancer," *Prostate*, Vol. 51, p. 108-116 (2002)). Moreover, a phase II clinical study of troglitazone treatment in patients with prostate cancer was associated with prolonged periods of stable disease characterized by the absence of new metastases or disease-related symptoms and lower PSA levels (Mueller et al., 2000). Troglitazone (available under the trade name **REZULIN** **REZULIN**[®] from Parke-Davis division of Warner-Lambert Company; Morris Plains, NJ) is a synthetic ligand that downregulates PSA mRNA expression.

Please replace the paragraph beginning at page 13, line 8, with the following rewritten paragraph:

The HER-kinase axis inhibitors used in connection with various embodiments of the present invention may exhibit anti-cancer properties. The HER-kinase axis inhibitor may be 2C4 or a 2C4 derivative, but may also include, without limitation, ansamycins, gefitinib (compound ZD1839 developed by AstraZeneca UK Ltd.; available under the tradename IRESSA IRESSA[®], hereinafter "IRESSA IRESSA[®]"), erlotinib (compound OSI-774 developed by Genentech, Inc. and OSI Pharmaceuticals, Inc.; available under the tradename TARCEVA TARCEVA[®]; hereinafter "TARCEVA TARCEVA[®]"), monoclonal antibodies, rapamycin, src (transforming gene of Rous sarcoma virus) inhibitors, tyrosine kinase inhibitors, LY294002 (available from Cayman Chemical), imatinib mesylate (available from Novartis Pharmaceuticals Corp. under the tradename GLEEVEC GLEEVEC[®]; hereinafter "GLEEVEC GLEEVEC[®]"), trastuzumab (available from Genentech, Inc. under the tradename HERCEPTIN HERCEPTIN[®]; hereinafter "HERCEPTIN HERCEPTIN[®]"), CI1033 (available from Pfizer Inc.), PKI166 (available from Novartis AG), GW2016 (available from GlaxoSmithKline), EKB569 (available from Wyeth), IMC-C225 (available from ImClone Systems Inc. and Bristol-Myers Squibb Co.), and pharmaceutical equivalents, derivatives and salts, as well as other functionally related compounds, although numerous other HER-kinase axis inhibitors may be used, as will be readily appreciated by those of skill in the art. For example, guidance as to particular HER-kinase axis inhibitors is provided in the literature and generally available to practitioners in the art. See, e.g., U.S. patent application No. 2002/0045570 (describing compositions for the inhibition of HER-family tyrosine kinases). As further described in the ensuing examples, 2C4 was found to inhibit MAP-kinase phosphorylation of PPAR γ , thereby preventing PPAR γ protein degradation, and it was generally well tolerated by recipients.

Please replace the paragraph beginning at page 22, line 25, with the following rewritten paragraph:

Total RNA was extracted from prostate tumors or the LNCaP cell line using the TRIZOL TRIZOL[®] reagent (obtained from Invitrogen Corp.; San Diego, CA). Samples

were heated at 95°C for 3 minutes and snap-cooled before proceeding with DNase I treatment to prevent RNA/DNA hybridization. DNase I (obtained from Ambion; Austin, TX) was used to remove any genomic DNA that might interfere with the reaction. Samples were treated with DNase I for 1 hour at 37 °C. The RNA yield was quantified spectrometrically.

Please replace the paragraphs beginning at page 25, line 7, with the following rewritten paragraphs:

For transfection, cells were grown in DMEM with 10% FBS for at least 24 hours prior to transfection. Transient transfections were performed in 12-well plates for at least 24 hours prior to transfection. At approximately 50% confluence, cells were transfected using the FuGENE FuGENE® transfection reagent (obtained from Roche Diagnostics GmbH; Mannheim, Germany) according to the manufacturer's instruction with 0.5 µg of reporter plasmid (AOx)₃-TK-Luc, 0.1 to 0.2 µg of control plasmid pCMXβgal, 0.1 µg PPAR γ expression plasmid and carrier DNA for a total of 1 µg DNA per well. After 16 hours, the cells were washed and fresh medium containing the appropriate amount of drugs, prepared in 0.5% DMSO, was added to the cells for another 24 hours. The cells were treated with either vehicle alone (DMSO), indomethacin, rosiglitazone or varying concentrations of R- or S-etodolac.

For luciferase assays, cells were lysed in potassium phosphate buffer containing 1% TRITON X-100 (obtained from Rohm and Haas Co.; Philadelphia, PA) and light emission was detected in the presence of luciferin using a microtiter plate luminometer. Luciferase values were normalized for variations in transfection efficiency using a β-galactosidase internal control. The results are expressed as relative luciferase units (RLU). The luciferase activity values represent the mean of a minimum of three independent transfections performed in triplicate.